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(54) Title: MESALAZINE CONTROLLED RELEASE ORAL PHARMACEUTICAL COMPOSITIONS

(57) Abstract: Controlled-release oral pharmaceutical compositions containing as active ingredient 5-amino-salicylic acid, comprising: a) an inner lipophilic matrix consisting of substances with melting point below 90 °C in which the active ingredient is at least partly inglobated; b) an outer hydrophilic matrix in which the lipophilic matrix is dispersed; c) optionally other excipients.

MESALAZINE CONTROLLED RELEASE ORAL PHARMACEUTICAL COMPOSITIONS

The present invention relates to controlled release oral pharmaceutical compositions containing as active ingredient 5-amino salicylic acid, also named mesalazine.

BACKGROUND OF THE INVENTION

Mesalazine is used in the treatment of Chron's disease and ulcerative colitis thanks to its antiinflammatory activity on the intestinal mucuses. Controlled-release formulations of mesalazine are disclosed in WO 95/16451, EP 0 453 001, EP 0 377 477.

The preparation of a sustained, controlled, delayed or anyhow modified release form can be carried out according to different known techniques:

1. The use of inert matrices, in which the main component of the matrix structure opposes some resistance to the penetration of the solvent due to the poor affinity towards aqueous fluids; such property being known as lipophilia.
2. The use of hydrophilic matrices, in which the main component of the matrix structure opposes high resistance to the progress of the solvent, in that the presence of strongly hydrophilic groups in its chains, mainly branched, remarkably increases viscosity inside the hydrated layer.
3. The use of bioerodible matrices, which are capable of being degraded by the enzymes of some biological compartment.

All the procedures listed above suffer, however, from drawbacks and imperfections.

Inert matrices, for example, generally entail non-linear, but esponential, release of the active ingredient.

Hydrophilic matrices have a linear behaviour until a

certain fraction of active ingredient has been released, then they significantly deviate from linear release.

Bioerodible matrices are ideal to carry out the so-called "site-release", but they involve the problem of finding the suitable enzyme or reactive to degradation. Furthermore, they frequently release in situ metabolites that are not wholly toxicologically inert.

A number of formulations based on inert lipophilic matrices have been described: Drug Dev. Ind. Pharm. 13 (6), 1001-1022, (1987) discloses a process making use of varying amounts of colloidal silica as a porization element for a lipophilic inert matrix in which the active ingredient is incorporated.

The same notion of canalization of an inert matrix is described in US 4,608,248 in which a small amount of a hydrophilic polymer is mixed with the substances forming an inert matrix, in a non sequential compenetration of different matrix materials.

EP 375,063 discloses a technique for the preparation of multiparticulate granules for the controlled-release of the active ingredient which comprises co-dissolution of polymers or suitable substances to form a inert matrix with the active ingredient and the subsequent deposition of said solution on an inert carrier which acts as the core of the device. Alternatively, the inert carrier is kneaded with the solution containing the inert polymer and the active ingredient, then the organic solvent used for the their dissolution is evaporated off to obtain a solid residue. The resulting structure is a "reservoir", i.e. is not macroscopically homogeneous along all the symmetry axis of the final form.

The same "reservoir" structure is also described in Chem. Pharm. Bull. 46 (3), 531-533,, (1998) which improves the application through an annealing technique of the inert

polymer layer which is deposited on the surface of the pellets.

To the "reservoir" structure also belong the products obtained according to the technique described in WO 93/00889 which discloses a process for the preparation of pellets in hydrophilic matrix which comprises:

- dissolution of the active ingredient with gastro-resistant hydrophilic polymers in organic solvents;
- drying of said suspension;
- subsequent kneading and formulation of the pellets in a hydrophilic or lipophilic matrix without distinction of effectiveness between the two types of application.

EP 0 453 001 discloses a multiparticulate with "reservoir" structure inserted in a hydrophilic matrix. The basic multiparticulate utilizes two coating membranes to decrease the release rate of the active ingredient, a pH-dependent membrane with the purpose of gastric protection and a pH-independent methacrylic membrane with the purpose of slowing down the penetration of the aqueous fluid.

WO 95/16451 discloses a composition only formed by a hydrophilic matrix coated with a gastro-resistant film for controlling the dissolution rate of mesalazine.

When preparing sustained-, controlled- release dosage forms of a medicament topically active in the gastrointestinal tract, it is important to ensure a controlled release from the first phases following administration, i.e. when the inert matrices have the maximum release rate inside the logarithmic phase, namely the higher deviation from linear release.

Said object has been attained by the present invention, which also allows to prepare compositions characterized by a high content in active ingredient.

DISCLOSURE OF THE INVENTION

The invention provides controlled release oral

pharmaceutical compositions containing 5-amino-salicylic acid as the active ingredient, comprising:

a) an inner lipophilic matrix consisting of substances with melting point below 90¢C in which the active ingredient is at least partially inglobated;

b) an outer hydrophilic matrix in which the lipophilic matrix is dispersed;

c) optionally other excipients.

DETAILED DISCLOSURE OF THE INVENTION

The compositions of the invention can be obtained with a method comprising the following steps:

a) the active ingredient is first inglobated in a low melting excipient or mixture of excipients, while heating to soften and/or melt the excipient itself, which thereby incorporates the active ingredient by simple dispersion.

After cooling at room temperature an inert matrix forms, which can be reduced in size to obtain matrix granules containing the active ingredient particles.

b) the inert matrix granules are subsequently mixed together with one or more hydrophilic water-swellable excipients.

This way, when the tablet is contacted with biological fluids, a high viscosity swollen layer is formed, which coordinates the solvent molecules and acts as a barrier to penetration of the aqueous fluid itself inside the new structure. Said barrier antagonizes the starting "burst effect" caused by the dissolution of the medicament inglobated inside the inert matrix, which is in its turn inside the hydrophilic matrix.

The lipophilic matrix consists of substances selected from unsaturated and/or hydrogenated fatty acids, salts, esters or amides thereof, fatty acids mono-, di- or triglycerids, waxes, ceramides, cholesterol derivatives or mixtures thereof having melting point within the range of 40

to 90°C.

If desired, a fatty acid calcium salt may be incorporated in the lipophilic matrix which is subsequently dispersed in a hydrophilic matrix prepared with alginic acid, thus remarkably increasing the hydrophilic matrix viscosity following penetration of the solvent front until contact with the lipophilic matrix granules dispersed inside.

The weight content of the active ingredient in the lipophilic matrix usually ranges from 5 to 95%.

The inert lipophilic matrix is reduced into granules by an extrusion and/or granulation process, or any other known processes which retain the homogeneous dispersion and matrix structure of the starting mixture.

The hydrophilic matrix consists of excipients known as hydrogels, i.e. substances which pass from the dry state to the hydrated one, undergo the so-called "molecular relaxation", namely a remarkable increase in mass and weight following the coordination of a large number of water molecules by the polar groups present in the polymeric chains of the excipients themselves.

Examples of hydrogels which can be used according to the invention are compounds selected from polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, natural or synthetic gums, alginic acid.

The lipophilic matrix granules containing the active ingredient are mixed the with hydrophilic compounds cited above in a weight ratio typically ranging from 100:0.5 to 100:20 (lipophilic matrix: hydrophilic matrix). Part of mesalazine can optionally be mixed with hydrophilic substances to provide compositions in which the active ingredient is dispersed both in the lipophilic and the

hydrophilic matrix, said compositions being preferably in the form of tablets, capsules and/or minitablets.

The compression of the mixture of lipophilic matrix, hydrogel-forming compounds and, optionally, active ingredient non inglobated in the lipophilic matrix, yields a macroscopically homogeneous structure in all its volume, namely a matrix containing a dispersion of the lipophilic granules in a hydrophilic matrix.

The tablets, capsules and/or minitablets obtainable according to the invention can optionally be subjected to known coating processes with a gastro-resistant film, consisting of for example polymers of methacrylic acids (Eudragit$^{(R)}$) or cellulose derivatives, such as cellulose acetophthalate.

The compositions of the invention can contain a high percentage of active ingredient compared with the total composition weight up to 95%, an advantageous characteristic in the case of mesalazine which requires rather high unitary doses.

In terms of dissolution characteristics, the compositions of the invention provide a release profile of the active ingredient more homogeneous than the traditional systems. In fact, the immediate penetration of water inside the superficial layer of the hydrophilic matrix and the consequent swelling due to the distension of the polymeric chains of the hydrogels, gives rise to a high viscosity hydrated front which prevents the further penetration of water, linearly slowing down the dissolution process to a well determined point which can be located at about half the thickness until the further penetration of water would cause the disintegration of the hydrophilic layer and therefore the release of the content which, consisting of lipophilic granules, however induces the diffusional mechanism typical of these structures and therefore further slows down the

dissolution profile of the active ingredient.

The following examples illustrate the invention in greater detail.

Example 1

770 g of 5-aminosalicylic acid are added in a kneader with 20 g of carnauba wax and 50 g of stearic acid with heating until homogeneous dispersion, then extruded into small granules while cold.

The inert matrix granules are loaded into a mixer in which 30 g of Carbopol 971P(R) and 65 g of hydroxypropyl methylcellulose are sequentially added.

After a first mixing step for homogeneously dispersing the powders, 60 g of microcrystalline cellulose and 5 g of magnesium stearate are added. After mixing, the final mixture is tabletted to unitary weight of 649 mg/tablet or 510 mg/tablet to obtain 500 and 400 mg dosages, respectively.

The resulting tablets are film-coated with cellulose acetophthalate or polymethacrylates and a plasticizer to provide gastric resistance and prevent the early release of product in the stomach.

The dissolution profile of these tablets shows the release of an active ingredient amount lower than 30% within the first hour of permanence in simulated enteric juice, an amount lower than 60% at the fourth hour and an amount lower than 90% at the eighth hour, thus proving that the double matrix effectively controls dissolution.

Example 2

1000 g of 5-aminosalicylic acid are added in a kneader with 10 g of carnauba wax and 20 g of stearic acid with heating until homogeneous dispersion, then extruded into small granules while cold or directly granulated in a high rate mixer.

The resulting granules are loaded into a mixer in which

80 g of hydroxypropyl methylcellulose and 12 g of sodium starch glycolate are sequentially added. After a first mixing step, 11 g of silica colloidal and 11 g of magnesium stearate are added. The final mixture is homogenized, then tabletted to a unitary weight of 1144 mg/tablet.

The resulting tablets are then film coated with polymethacrylates or cellulose acetophthalate and plasticizers to provide gastric resistance.

The dissolution profile of these tablets after a lag time of permanence in the stomach and partly in the intestine provides the release of no more than 30% within the first hour, no more than 55% within two hours, no more than 70% within four hours, no more than 90% within eight hours.

Example 3

850 g of 5-aminosalicylic acid are added in granulator/kneader with 9 g of beeswax and 22 g of palmitic acid with heating, until homogeneous dispersion; then worked to a granulate in a high shear granulating device. The resulting granules are then loaded into a mixer which is added in succession with 45.5 g of hydroxypropyl methylcellulose, 45.5 g of microcrystalline cellulose, 20 g of sodium starch glycolate, 22 g of colloidal silica and 22 g of magnesium stearate. After homogenization, the final mixture is tabletted to a unitary weight of 975 mg/tablet.

The resulting tablets are then film coated with polymethacrylates or acetophthalate of cellulose and plasticizers to provide gastric resistance.

The dissolution profile of these tablets after a lag time of permanence in the stomach and partly in the intestine provides the release of no more than 30% within the first hour, no more than 50% within two hours, no more than 70% within four hours, no more than 90% within eight hours.

Example 4

1100 g of 5-aminosalicylic acid are added in granulator/kneader with 10 g of wax carnauba and 20 g of stearic acid.

10 g of polyacrylamide, 39.5 of microcrystalline cellulose and 22 g of colloidal silica are separately loaded into the homogenizer/granulator to obtain a homogeneous solid mixture, which is placed in the mixer where the active ingredient has been granulated and homogenized. 49.5 g of hydroxypropyl methylcellulose and 12 g of sodium alginate are thoroughly mixed, then added with 5 g of calcium carbonate, 34.5 g of microcrystalline cellulose and 11 g of magnesium stearate. The mixture is homogenized, then tabletted to a final unitary weight of 1194 mg/tablet. The resulting tablets are then film-coated with polymethacrylates or cellulose acetophthalate and plasticizers to provide gastric resistance.

The dissolution profile of these tablets after a lag time of permanence in the stomach and partly in the intestine provides the release of no more than 35% within the first hour, no more than 50% within two hours, no more than 70% within four hours, no more than 90% within eight hours.

Example 5

1200 g of 5-aminosalicylic acid are added in mixer with 10 g of carnauba wax and 20 g of stearic acid, with heating until homogeneous dispersion, then cold extruded into small granules or directly granulated in the high rate mixer.

The resulting granules are loaded into a mixer, then 70 g of hydroxypropyl methylcellulose and 20 g of sodium starch glycolate are sequentially added.

After a first mixing step, 80 g of sodium carbonate and 5 g of magnesium stearate are added. The final mixture is homogenized, then tabletted to unitary weight of 1375

mg/tablet.

The resulting tablets are then film-coated with polymethacrylates or cellulose acetophthalate and plasticizers to provide gastric resistance.

The dissolution profile of these tablets after a lag time of permanence in the stomach and partly in the intestine provides the release of no more than 30% within the first hour, no more than 50% within two hours, no more than 70% within four hours, no more than 90% within eight hours.

CLAIMS

1 Controlled-release oral pharmaceutical compositions containing as active ingredient 5-amino-salicylic acid, comprising:

a) an inner lipophilic matrix consisting of substances with melting point below 90°C in which the active ingredient is at least partly inglobated;

b) an outer hydrophilic matrix in which the lipophilic matrix is dispersed;

c) optionally other excipients.

2. Compositions as claimed in claim 1, wherein the lipophilic matrix consists of compounds selected from unsaturated and/or hydrogenated fatty acids, salts, esters or amides thereof, fatty acid mono-, di- or triglycerids, waxes, ceramides, cholesterol derivatives.

3. Compositions as claimed in claim 1 or 2, wherein 5-aminosalicylic acid is inglobated in the molten lipophilic matrix by kneading, extrusion and/or granulation.

4. Compositions as claimed in any one of the above claims, wherein the hydrophilic matrix consists of hydrogel-forming compounds.

5. Compositions as claimed in claim 4 wherein the hydrophilic matrix consists of compounds selected from polymers or copolymers of acrylic or methacrylic acid, alkylvinyl polymers, hydroxyalkyl celluloses, carboxyalkyl celluloses, polysaccharides, dextrins, pectins, starches and derivatives, alginic acid, natural or synthetic gums.

6. Compositions as claimed in any one of the above claims, comprising a gastro-resistant outer coating.

7. Compositions as claimed in claim 6, wherein the gastro-resistant coating consists of methacrylic acid polymers or cellulose derivatives.

8. Compositions as claimed in any one of the above claims,

in the form of tablets, capsules, minitablets, wherein the active ingredient is completely contained inside the lipophilic matrix.

9. Compositions as claimed in any one of claims 1 to 7, in the form of tablets, capsules, minitablets, wherein the active ingredient is dispersed both in the hydrophilic matrix and the lipophilic matrix.

10. Compositions as claimed in any one of the above claims, wherein the percentage of the active ingredient on the total composition weight ranges from 80 to 95%

11. A process for the preparation of the compositions of claims 1-10, which comprises:

a) melt granulation of at least one portion of the active ingredient with the lipophilic excipients with melting point lower than 90°C;

b) mixing the granules from step a) with the hydrophilic excipients and subsequent tabletting or compression.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/05321

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/20 A61K31/606

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 245 492 A (ZAMBON SPA) 8 January 1992 (1992-01-08) page 1, line 4 - line 7 page 2, line 11 - line 24 page 6, line 23 -page 8, last line page 10, line 2 page 12, line 13 - line 26; claims; examples 1,16	1,2,4-10
A	WO 98 26767 A (BUSETTI CESARE ;CRIMELLA TIZIANO (IT); OLGIATI VINCENZO (IT); POLI) 25 June 1998 (1998-06-25) page 3, line 16 -page 4, line 15 page 5, line 12 -page 7, line 19 page 8, line 23 -page 9, line 22; claims; examples 1,2	1-10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Int ational Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 851 555 A (PRIOR DAVID V ET AL) 22 December 1998 (1998-12-22) column 2, line 34 - line 36 column 2, line 64 -column 3, line 21 column 4, line 10 - line 18; claims 1-12; example 1	1-11
A	US 5 593 690 A (AKIYAMA YOHKO ET AL) 14 January 1997 (1997-01-14) column 1, line 34 -column 2, line 34; claims 1-4 column 3, line 46 -column 4, line 22; examples 23-25	1-11

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Intr tional Application No
PCT/EP 00/05321

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2245492 A	08-01-1992	IT 1244867 B	12-09-1994
		IT 1244037 B	28-06-1994
		AT 400295 B	27-11-1995
		AT 131091 A	15-04-1995
		AU 638583 B	01-07-1993
		AU 8019991 A	09-01-1992
		BE 1004882 A	16-02-1993
		CA 2044398 A	05-01-1992
		CH 683498 A	31-03-1994
		DE 4122039 A	09-01-1992
		DK 129591 A	05-01-1992
		ES 2036457 B	01-03-1994
		FI 913248 A	05-01-1992
		FR 2664163 A	10-01-1992
		GR 91100283 A,B	26-08-1992
		HU 59591 A	29-06-1992
		HU 9500435 A	28-09-1995
		IE 61651 B	16-11-1994
		IL 98525 A	23-07-1996
		JP 6024961 A	01-02-1994
		LU 87964 A	03-03-1992
		NL 9101161 A	03-02-1992
		NO 304579 B	18-01-1999
		PT 98188 A,B	29-05-1992
		SE 512373 C	06-03-2000
		SE 9102072 A	05-01-1992
		RU 2012330 C	15-05-1994
		US 5310558 A	10-05-1994
		US 5445828 A	29-08-1995
		US 5629017 A	13-05-1997
		ZA 9104724 A	27-05-1992
WO 9826767 A	25-06-1998	AU 5775398 A	15-07-1998
US 5851555 A	22-12-1998	AU 7578598 A	08-03-1999
		EP 0994699 A	26-04-2000
		WO 9908661 A	25-02-1999
US 5593690 A	14-01-1997	US 5399357 A	21-03-1995
		AT 106239 T	15-06-1994
		AU 3856193 A	26-08-1993
		AU 645003 B	06-01-1994
		AU 4443789 A	21-06-1990
		CA 2002363 A	08-05-1990
		DE 68915695 D	07-07-1994
		DE 68915695 T	15-09-1994
		DK 555389 A	09-05-1990
		EP 0368247 A	16-05-1990
		HU 9500640 A	28-11-1995
		JP 2223533 A	05-09-1990
		JP 2893191 B	17-05-1999
		KR 148002 B	17-08-1998
		NZ 231281 A	29-01-1991
		ZA 8908470 A	25-07-1990